IMPROVED SYNTHESIS OF DIHYDROISOQUINOLINE REISSERT COMPOUNDS

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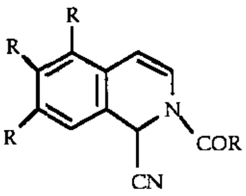
Abstract - Conversion of a series of 3,4-dihydroisoquinolines to their corresponding Reissert compounds was improved significantly over the usual reaction conditions by buffering the reaction medium at pH 8.

The formation of isoquinoline type Reissert compounds (**1**) from the reaction of an isoquinoline with an acid halide and cyanide ion has been studied extensively. Compounds of this type have found wide application in the synthesis of isoquinoline alkaloids and related compounds.[1,2] However, only a few examples of 3,4-dihydroisoquinoline Reissert compounds, (**2**) have been described.[3-6]



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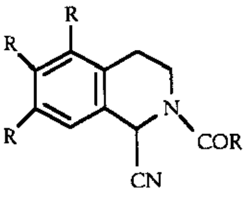

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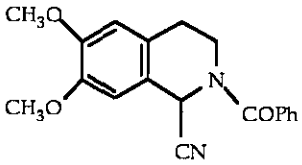
In connection with other work being done in our laboratory, we needed to prepare 2-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinaldonitrile (**3**). This compound has been prepared previously by two standard procedures. The first (1 : 2 : 3 ratio of substrate : PhCOCl : NaCN) gave a yield of 18%;[7] the second (1 : 3 : 4.5 ratio of substrate : PhCOCl : NaCN) gave a yield of 67%.[8]



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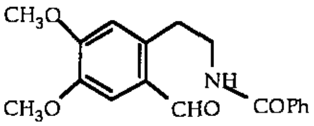

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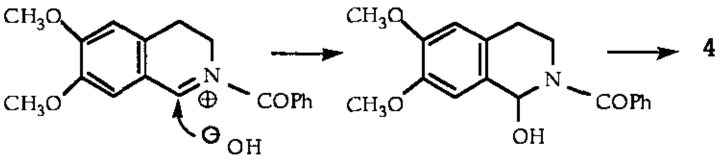
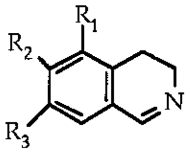
In repeating the second procedure, we obtained Reissert compound (**3**) in a maximum yield of 40%, together with aldehyde (**4**) in about 30% yield. Compounds (**3**) and (**4**) co-crystallized from the crude mixture but could be separated by recrystallization. Aldehyde (**4**) clearly results from the attack of hydroxide ion on the intermediate iminium ion, followed by ring opening of the resulting acyl carbinolamine (Scheme 1). In order to decrease the concentration of hydroxide ion, the pH of the sodium cyanide solution was adjusted from an initial value of 10 to 8 prior to addition to the reaction mixture. We found the yield of Reissert compound to improve significantly, with none of the aldehyde being formed. Buffering the system at pH 8 with bicarbonate resulted in even higher yields of the desired product.



Scheme 1

We then compared the behavior of the three dihydroisoquinolines (**6**, **7** and **8**) under our conditions (Method A) with that of the same substrates under the standard reaction conditions. (Method B). The results are shown in Table 1. Method A gives consistently much better yields of the Reissert compounds, with no formation of aldehyde by-products.

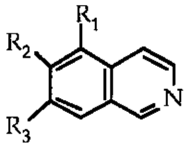
The corresponding isoquinolines (**9** - **11**) were also investigated as substrates. No aldehydes or carbinolamines were found when either method was used. Surprisingly, however, under the conditions of method A, lower yields were obtained and much unreacted starting material was recovered even when the reaction time was extended to 24 hours. This difference in behavior may be attributed to the weaker basicity and greater stability of the fully aromatic system as compared with the dihydro compounds. The isoquinolines then, under conditions of Reissert compound formation, react more slowly with benzoyl chloride to produce the quaternary salt, which also is attacked to a considerable extent at the carbonyl carbon by the nucleophiles present to regenerate the isoquinoline. An excess of reagents (i.e. Method B) is therefore required for the irreversible formation of the Reissert products.



6 $R_1 = R_2 = R_3 = H$

7 $R_1 = H; R_2 = R_3 = OMe$

8 $R_1 = R_2 = R_3 = OMe$



9 $R_1 = R_2 = R_3 = H$

10 $R_1 = H; R_2 = R_3 = OMe$

11 $R_1 = R_2 = R_3 = OMe$

Substrate	Method[a]	Reaction Time (h)	% Yield RC	% Yield Ald.
6	A	2	65	-
6	B	4	-	40
7	A	2	80	-
7	B	4	40	30
8	A	2	68[b]	-
8	B	4	19	35
9	A	24	48	-
9	B	4	69	-
10	A	24	38	-
10	B	4	65	-
11	A	4	38	-
11	B	4	82	-

Table 1. RC = Reissert Compound, Ald. = aldehyde.

[a] Method A: substrate : PhCOCl : NaCN - 1 : 1.5 : 2; buffered at pH 8 ($NaHCO_3$);
Method B: substrate : PhCOCl : NaCN - 1 : 3 : 4.5.

[b] This new compound (mp 121-122 °C) gave satisfactory spectral data:
m/z (rel. intensity) 352 (100)(M^+), exact mass calcd for $C_{20}H_{20}N_2O_4$ 352.1423, found 352.1412.

EXPERIMENTAL

General Procedure for Synthesis of Dihydroisoquinoline Reissert Compounds.

The pH of a solution of sodium cyanide (103 mg, 2.1 mmol) in water (0.5 ml) was adjusted from 10 to 8 using conc. HCl (caution: HCN). This was added to a cold (ice-bath) mixture of dihydroisoquinoline (1.05 mmol) and sodium bicarbonate (400 mg, 4.8 mmol) in methylene chloride (4 ml). Benzoyl chloride (0.18 ml, 1.58 mmol) in methylene chloride (1 ml) was then added dropwise with vigorous stirring over 30 min, then stirring was continued for an additional 90 min while allowing the mixture to warm to room temperature. Water (10 ml) was added, the layers were separated, and the aqueous solution was extracted with methylene chloride (1 x 8 ml).

The combined organic phases were washed with 10% HCl (2 x 8 ml), 10% NaOH (2 x 8 ml) and water (2 x 8 ml), then dried (Na_2SO_4) and concentrated. The resulting oil or semi-solid was treated with hexane, then triturated with methanol (or ethanol) to yield the crude Reissert compound, which was finally recrystallized from methanol (or ethanol).

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